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DECISION ON APPEAL

This is an appeal from the Examiner’s rejection under 35 U.S.C. §§ 102 and 103 of claims directed to methods of treating Huntington’s disease with carbenoxolone. We have jurisdiction for this appeal under 35 U.S.C. § 6(b). The rejections are reversed, but new grounds of rejection are set forth pursuant to 37 C.F.R. § 41.50(b).

1 The Appeal Brief (“Appeal Br.”) lists Massachusetts Institute of Technology as the real party in interest and states that Oxalys Pharmaceuticals, Inc., a Canadian corporation, is an exclusive licensee of the application.
2 “The ’854 Application.”
STATEMENT OF CASE

The claims stand finally rejected by the Examiner as follows:


Independent claim 1, which is illustrative of the appealed subject matter, reads as follows:

1. A method for treating Huntington's disease, comprising administering to a subject having Huntington's disease, an effective amount of carbenoxolone or 18β-Glycyrrhetinic acid, or an analog, salt, or solvate thereof, thereby treating the subject having Huntington's disease.

REJECTIONS

Claim 1 is directed to administering “an effective amount of carbenoxolone or 18β-Glycyrrhetinic acid, or an analog, salt, or solvate thereof” to treat a subject having Huntington’s disease. Carbenoxolone is an analog of 18β-Glycyrrhetinic acid. Spec. 28; 27–28; 65:23–24.

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3 The publication date of Cohen is after the priority date of April 15, 2011 accorded to the rejected claims. However, the priority dates of the Cohen application are March 1, 2011 and March 29, 2011.
In response to a requirement to elect a species of claim 1, Appellants elected carbenoxolone. Response to Species Election Requirement 2 (May 13, 2014). Appellants stated in the Appeal Brief that claim 93, directed to the non-elected 18β-Glycyrrhetinic acid species, was “rejoined without reason or comment by the Examiner in the Office Action mailed on May 18, 2015.” Appeal Br. 3 (fn. 2). While the Examiner did not directly respond to Appellants’ statement, the Examiner stated in the Answer that the elected species is carbenoxolone (Ans. 2), consistent with the Examiner’s position throughout prosecution (Final Act. 2–3). Consequently, we consider carbenoxolone to be the elected species and the subject of this appeal. Claim 92 is directed to treatment with the elected species carbenoxolone. Claim 93 is directed to treatment with 18β-Glycyrrhetinic acid; however, this is unelected subject matter, despite being included in the statement of the rejection.

All three of the appealed rejections are based on the Examiner’s findings that each of Oksenberg, Wilckens, and Cohen describe treating Huntington’s disease with carbenoxolone. Ans. 3, 4, and 5. The Examiner cited Oksenberg’s disclosure as anticipatory to the claims, and Wilckens and Cohen as rendering the claims obvious because the Examiner found that the selection of Huntington’s disease and carbenoxolone from the lists in Wilckens and Cohen was necessary to have arrived at the claimed subject matter. Id. Shao was cited by the Examiner as evidence that Huntington’s disease is a polyglutamine disease which expresses the Huntingtin protein having a polyQ tract of 36-121 residues, a limitation recited in some of the dependent claims. Id. 3.
In response to the rejections, Appellants provided a declaration by Katharine Sepp, Ph.D. (“Sepp Decl.”), a co-inventor of the ’854 Application. Sepp Decl. ¶ 2. Dr. Sepp provided evidence in her declaration that carbenoxolone is toxic at the intraperitoneal and intravenous dosages utilized in Oksenberg. Id. ¶¶ 28–32. Dr. Sepp also stated in her declaration that the skilled worker, reading Oksenberg, Wilckens, and Cohen, would have considered “whether the prophetic treatments disclosed therein are viable, taking into consideration various factors that include pharmacological considerations such as . . . toxicology profiles.” Id. ¶ 17. Dr. Sepp also provided evidence that carbenoxolone does not cross the blood brain barrier. Id. ¶¶ 34–37.

Oksenberg Rejection

Dr. Sepp provided factual evidence, including citing several publications, that the amounts of carbenoxolone administered to rats in Example 2 of Oksenberg were at a toxic dose level. Sepp Decl. ¶¶ 28–32. Example 2 of Oksenberg is model of cerebral ischemia. Oksenberg ¶ 117. Dr. Sepp further testified in her declaration that “[b]ased on the description and data in Oksenberg, a skilled artisan would thus not conclude that a toxic level carbenoxolone dose which shows histological ‘neuroprotection’ could provide functional ‘neuroprotective’ effects in a live animal.” Sepp Decl. ¶ 31. Dr. Sepp also cited a post-filing publication co-authored by Oksenberg that carbenoxolone results in complete lethality of all animals within 7 days post-treatment when used to treat ischemia in rats. Id. Dr. Sepp stated that in light of the “knowledge of carbenoxolone toxicology and ‘neuroprotective’ anti-ischemic dose ranges,” the skilled worker would not
have read Oksenberg as teaching “the use of carbenoxolone as a ‘neuroprotective’ drug for the treatment of HD [Huntington’s disease], especially since HD is a genetic and chronic neurodegenerative disease that would require a chronic dosing of a drug that only achieves its therapeutic effect at a lethal toxic level in the model system employed by Oksenberg.” *Id.* ¶ 32. Thus, Appellants argue that “Oksenberg is not an operable disclosure because the dosage shown to provide neuroprotective effects in the ischemia model was well known in the art to be toxic and lethal to rodents.” Appeal Br. 7.

The Examiner stated that “Appellant has provided nothing more than allegations in the absence of facts to support his assertion that Oksenberg is not enabled for the treatment of Huntington’s disease.” Ans. 7–8.

We do not agree with the Examiner on this point. Dr. Sepp cited specific evidence in her declaration, including several pre-filing date publications, of the toxicity of carbenoxolone and explained why such knowledge would not have led the skilled worker to read Oksenberg as teaching how to use the drug to treat Huntington’s disease. Thus, the guidance described in Oksenberg for administering carbenoxolone to treat Huntington’s disease would not have necessarily led to success in its treatment because the dosages indicated in Example 2 of Oksenberg could have been toxic. Anticipation “may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.” *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (internal citation and quotation marks omitted).

Because the Examiner did not provide adequate reason or evidence to disbelieve or discredit Dr. Sepp’s declaration, we conclude that Oksenberg is
not enabled for the claimed method treating Huntington’s disease with carbenoxolone.

The rejection of claims 1, 4, 5, 9, 10, 92, 94, 98, and 99 as anticipated by Oksenberg is reversed.

OBVIOUSNESS BASED ON WILCKENS AND COHEN

The rejections relying on Wilckens and Cohen are based on the obviousness of utilizing carbenoxolone to treat Huntington’s disease. It is not disputed that both publications describe the drug and its use to treat disease. Ans. 4, 5.

Appellants contend that it would not have been obvious to treat Huntington’s disease with carbenoxolone “because it is well established that parenterally-dosed carbenoxolone does not penetrate the brain in detectible quantities.” Appeal Br. 16. The underlying premise of this argument is that carbenoxolone must cross the blood brain barrier to have its therapeutic effect. The ’854 Application discloses that carbenoxolone targets 11-beta-hydroxysteroid dehydrogenase 1 (HSD1), “a brain enzyme that regulates the production of cortisol in the brain” (’854 App. 31:67), which is consistent with the premise that the drug must cross the blood barrier to treat Huntington’s disease. Accordingly, because this issue was not disputed by either the Examiner or Appellants, for the purpose of deciding this appeal, we adopt the finding that carbenoxolone must cross the blood barrier to treat Huntington’s disease.

Dr. Sepp provided evidence that carbenoxolone was known at the time of the invention not to cross the blood brain barrier. Sepp Decl. ¶ 34–37. Based on this evidence, Dr. Sepp stated:
[A] skilled artisan would not deem Wilckens as teaching a viable treatment of HD, owing to the known pharmacological properties of carbenoxolone indicating that it cannot penetrate the blood-brain barrier to inhibit the HSD 1 enzyme and thereby elicit a beneficial effect in the brain.

*Id.* ¶ 38. Dr. Sepp made a similar statement about Cohen. *Id.* ¶¶ 45, 46.

The Examiner did not find this argument persuasive because of statements in the Specification by the inventors that carbenoxolone can cross the blood brain barrier. Ans. 8 (citing 31:15–16 and 43:19 of the ’854 Application). However, the statements in the ’854 Application referenced by the Examiner are not supported by factual evidence that it was known at the time of the invention that carbenoxolone could cross the blood brain barrier. As discussed by Dr. Sepp, there is evidence that it did not. Sepp Decl. ¶¶ 34–37. For example, the publication by Takeuchi, cited by Appellants, states that carbenoxolone disodium “hardly penetrate[s] the BBB [blood brain barrier].” Takeuchi 2. The publication by Leshchenko also concluded that carbenoxolone does not cross the blood brain barrier. Leshchenko cited an earlier study which suggested that carbenoxolone did cross the blood brain barrier, but explained that the earlier study only had indirect evidence of this, and their own work showed that carbenoxolone did not penetrate the blood brain barrier. Leshchenko 2. Thus, based on the evidence before us, we conclude that it would not have been reasonably expected that carbenoxolone, when administered systemically and outside

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4 Takeuchi et al., *PLoS ONE*, June 2011, 6(6): 1-13 (e21108). Takeuchi was published June 21, 2001, which is after the priority date of April 15, 2011 accorded by the Examiner. However, it relies on earlier publications for this fact.

the blood brain barrier, would treat Huntington’s disease. An obviousness determination requires finding both that a skilled artisan would have been motivated to combine the teachings of the prior art and that the skilled artisan would have had a reasonable expectation of success in doing so. Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd., 821 F.3d 1359, 1367 (Fed. Cir. 2016).

Accordingly, we reverse both obviousness rejections based on Wilckens and Cohen because the Examiner did not establish there would have been a reasonable expectation of success that carbenoxolone could be used to treat Huntington’s disease.

NEW GROUNDS OF REJECTION

Leshchenko, however, suggested intracerebral injection of carbenoxolone to circumvent the inability of carbenoxolone to cross the blood brain barrier. Leshchenko 2. Leshchenko teaches:

Hence, intracerebral injections are strongly recommended if the study is concerned with possible brain effects of the drug. In addition, intracerebral administration circumvents the potential confounding factor of systemic effects, which may be mediated by mineralocorticoid receptor activation and could contribute to the observed results.

Id.

Independent claim 1 does not exclude intracerebral injection of carbenoxolone as suggested by Leshchenko. Consequently, based on Leshchenko, one of ordinary skill in the art would have had reason to administer carbenoxolone by intracerebral injection to circumvent the blood brain barrier and to avoid carbenoxolone toxicity when administered by intraperitoneal or intravenous injection (Sepp Decl. ¶ 28).
Accordingly, the subject matter of claims 1 and 92 would have been obvious to one of ordinary skill in the art based on (1) Wilckens and Leshchenko, as evidenced by Shao; (2) Cohen and Leshchenko, as evidenced by Shao; and (3) Oksenberg and Leshchenko, as evidenced by Shao. Because the rationale differs from the Examiner’s, and Leshchenko is newly cited in the rejection, the rejections are set forth as new grounds pursuant 37 C.F.R. §41.50(b).

We leave it to the Examiner to determine the obviousness of the dependent claims. However, we note that claims 9 and 98 are limited to oral administration. Dr. Sepp’s declaration establishes that one of ordinary skill in the art would not have administered carbenoxolone orally or other systemic routes because of its inability to cross the blood brain barrier.

The new grounds of rejection are as follows:

Claims 1 and 92 are rejected under 35 U.S.C. 103(a) as obvious in view of Wilckens and Leshchenko, as evidenced by Shao.

Claims 1 and 92 are rejected under 35 U.S.C. 103(a) as obvious in view of Cohen and Leshchenko, as evidenced by Shao.

Claims 1 and 92 are rejected under 35 U.S.C. 103(a) as obvious in view of Oksenberg and Leshchenko, as evidenced by Shao.

TIME PERIOD FOR RESPONSE

This Decision contains a new ground of rejection pursuant to 37 C.F.R. §41.50(b). Section 41.50(b) provides “[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review.” Section 41.50(b) also provides:
When the Board enters such a non-final decision, the appellant, within two months from the date of the decision, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

(1) Reopen prosecution. Submit an appropriate amendment of the claims so rejected or new Evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the prosecution will be remanded to the examiner. The new ground of rejection is binding upon the examiner unless an amendment or new Evidence not previously of Record is made which, in the opinion of the examiner, overcomes the new ground of rejection designated in the decision. Should the examiner reject the claims, appellant may again appeal to the Board pursuant to this subpart.

(2) Request rehearing. Request that the proceeding be reheard under § 41.52 by the Board upon the same Record. The request for rehearing must address any new ground of rejection and state with particularity the points believed to have been misapprehended or overlooked in entering the new ground of rejection and also state all other grounds upon which rehearing is sought.

Further guidance on responding to a new ground of rejection can be found in the MPEP § 1214.01.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1). See 37 C.F.R. §§ 41.50(f), 41.52(b).

REVERSED
37 C.F.R. § 41.50(b)